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PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 03 November 1999 (03.11.99)	
International application No. PCT/GB99/00511	**Applicant's or agent's file reference** 545P78531
International filing date (day/month/year) 18 February 1999 (18.02.99)	**Priority date** (day/month/year) 18 February 1998 (18.02.98)
Applicant BEIJNEN, Jacob, Hendrik et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

13 September 1999 (13.09.99)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Juan Cruz

Telephone No.: (41-22) 338.83.38

2931363

Copy for the Elected Office (EO/US)

PCT/GB99/0051

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

To:

RUFFLES, Graham, Keith
Marks & Clerk
57-60 Lincoln's Inn Fields
London WC2A 3LS
ROYAUME-UNI

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

Date of mailing (day/month/year) 23 August 2000 (23.08.00)	
Applicant's or agent's file reference 545P78531	**IMPORTANT NOTIFICATION**
International application No. PCT/GB99/00511	**International filing date** (day/month/year) 18 February 1999 (18.02.99)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
RUFFLES, Graham, Keith 57-60 Lincoln's Inn Fields London WC2A 3LS United Kingdom	GB	GB
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
RUFFLES, Graham, Keith 57-60 Lincoln's Inn Fields London WC2A 3LS United Kingdom	GB	GB
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:
The above-mentioned applicant should now be recorded as applicant for the purposes of Sudan (SD) only.

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[ ] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Dominique DELMAS
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

Form PCT/IB/306 (March 1994)

003483347

Copy for the Elected Office (EO/US)

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

RUFFLES, Graham, Keith
Marks & Clerk
57-60 Lincoln's Inn Fields
London WC2A 3LS
ROYAUME-UNI

Date of mailing (day/month/year)
23 August 2000 (23.08.00)

Applicant's or agent's file reference
545P78531

IMPORTANT NOTIFICATION

International application No.
PCT/GB99/00511

International filing date (day/month/year)
18 February 1999 (18.02.99)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address
PHARMA MAR, S.A.
Poligono Industrial de Tres Cantos
Calle de la Calera, 3
E-28760 Tres Cantos
Spain

State of Nationality: ES
State of Residence: ES
Telephone No.:
Facsimile No.:
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address
PHARMA MAR, S.A.
Poligono Industrial de Tres Cantos
Calle de la Calera, 3
E-28760 Tres Cantos
Spain

State of Nationality: ES
State of Residence: ES
Telephone No.:
Facsimile No.:
Teleprinter No.:

3. Further observations, if necessary:
The above-mentioned applicant should now be recorded as applicant for all designated States except the United States of America (US) and Sudan (SD).

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[ ] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

Authorized officer
Dominique DELMAS
Telephone No.: (41-22) 338.83.38

003483346

TENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
545P78531		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/GB 99/ 00511	18/02/1999	18/02/1998
Applicant		
PHARMA MAR, S.A. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 2 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established by this Authority to read as follows:

   PHARMACEUTICAL FORMULATION OF A DIDEMNIN COMPOUND

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. --

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
GB 99/00511

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K38/15 A61K9/08 A61K9/19

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 048 149 A (UNIVERSITY OF ILLINOIS FOUNDATION) 24 March 1982 (1982-03-24) page 8, line 1 - line 4; example 6 page 18, line 29 - page 19, line 6 & US 5 294 603 A cited in the application	1-11
A	US 4 670 262 A (G. BATTELLI ET AL.) 2 June 1987 (1987-06-02) column 2, line 20 - line 29; claims 1,8,9; example III	1-11
A	US 5 462 726 A (N.J. LODGE) 31 October 1995 (1995-10-31) column 5, line 62 - line 66; claims 1-5; example 4	1-11

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 July 1999	30/07/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Ryckebosch, A

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
[redacted]/GB 99/00511

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 48149 A	24-03-1982	JP 1684261 C	31-07-1992
		JP 3049919 B	31-07-1991
		JP 57081413 A	21-05-1982
		US 4950649 A	21-08-1990
		US 4782135 A	01-11-1988
		US 5137870 A	11-08-1992
		US 4493796 A	15-01-1985
		US 5294603 A	15-03-1994
		US 4548814 A	22-10-1985
US 4670262 A	02-06-1987	AT 382077 B	12-01-1987
		AU 559499 B	12-03-1987
		AU 1908983 A	29-03-1984
		BE 897761 A	02-01-1984
		CA 1211372 A	16-09-1986
		CH 655852 A	30-05-1986
		DE 3333024 A	29-03-1984
		DK 424383 A,B,	24-03-1984
		FI 833300 A,B,	24-03-1984
		FR 2533439 A	30-03-1984
		GB 2127291 A,B	11-04-1984
		GR 79055 A	02-10-1984
		IE 56173 B	08-05-1991
		JP 59078117 A	04-05-1984
		NL 8303211 A	16-04-1984
		SE 464061 B	04-03-1991
		SE 8304920 A	24-03-1984
		SU 1424722 A	15-09-1988
		ZA 8306904 A	31-10-1984
US 5462726 A	31-10-1995	NONE	

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
545P78531		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB99/00511	18/02/1999	18/02/1998

International Patent Classification (IPC) or national classification and IPC
A61K38/15

Applicant
PHARMA MAR, S.A. et al.

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
13/09/1999	18. 11. 99

Name and mailing address of the international preliminary examining authority:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized officer

Cattell, James

Telephone No. +49 89 2399 8468

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB99/00511

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-6 as originally filed

Claims, No.:

1-11 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-11
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-11
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-11
	No:	Claims	

2. Citations and explanations

see separate sheet

1). Document D1 (EP-A-0,048,49) describes on page 18 lines 18 to 27 and examples 5,6 and 8 the problems associated with didemnin preparations. Only the water soluble forms are prepared as a solution. The use of mixed solvents is not disclosed.

The successful use of such solvent systems, specifically for didemnin compounds, could not have been predicted from the prior art (Art 33(3) PCT).

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* 545P78531

Box No. I TITLE OF INVENTION

Pharmaceutical Formulation

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

Pharma Mar, S.A.
Calle de la Calera, 3
Polígono Industrial de Tres Cantos
28760 Tres Cantos
Madrid
Spain

☐ This person is also inventor.

Telephone No.

Facsimile No.

Teleprinter No.

State *(that is, country)* of nationality: ES

State *(that is, country)* of residence: ES

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☒ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

Ruffles, Graham Keith
57-60 Lincoln's Inn Fields
London WC2A 3LS.
United Kingdom

This person is:

☒ applicant only

☐ applicant and inventor

☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is,country)* of nationality: GB

State *(that is, country)* of residence: GB

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☒ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

Ruffles, Graham Keith
Marks & Clerk
57-60 Lincoln's Inn Fields
London WC2A 3LS.
United Kingdom

Telephone No.
0171-400-3000

Facsimile No.
0171-404-4910

Teleprinter No.
25311 EMANDC G

☐ Adress for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

See Notes to the request form

Continuation of Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

Beijnen, Jacob Hendrik
The Netherland Cancer Institute/Slotervaart Hospital
Department of Pharmacology
Louwesweg 6
1066 EC Amsterdam
The Netherlands

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: NL

State *(that is, country)* of residence: NL

This person is applicant for the purposes of:
- ☐ all designated States
- ☐ all designated States except the United States of America
- ☒ the United States of America only
- ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

Nuyen, Bastiaan
The Netherland Cancer Institue/Slotervaart Hospital
Department of Pharmacology
Louwesweg 6
1066 EC Amsterdam
The Netherlands

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: NL

State *(that is, country)* of residence: NL

This person is applicant for the purposes of:
- ☐ all designated States
- ☐ all designated States except the United States of America
- ☒ the United States of America only
- ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

Henrar, Roland Elizabeth Cornelis
New Drug Development Office (NDDO)
Free University Hospital
Gebouw Zuid
Amstelveenseweg 601
1081 JC Amsterdam, The Netherlands

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: NL

State *(that is, country)* of residence: NL

This person is applicant for the purposes of:
- ☐ all designated States
- ☐ all designated States except the United States of America
- ☒ the United States of America only
- ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

Gomez, Andres
Pharma Mar, S.A.
Calle de la Calera, 3
Poligono Industrial de Tres Cantos
28760 Tres Cantos
Madrid, Spain

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: ES

State *(that is, country)* of residence: ES

This person is applicant for the purposes of:
- ☐ all designated States
- ☐ all designated States except the United States of America
- ☒ the United States of America only
- ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Sheet No. 3 ......

Continuation of Box No. III **FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS**

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

Jimeno, Jose
Pharma Mar, S.A.
Calle de la Calera, 3
Poligono Industrial de Tres Cantos
28760 Tres Cantos
Madrid, Spain

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: ES

State *(that is, country)* of residence: ES

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked)*:

Regional Patent

- [X] AP ARIPO Patent: GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, SD Sudan, SZ Swaziland, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- [X] EA Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- [X] EP European Patent: AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- [X] OA OAPI Patent: BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

- [X] AL Albania .....
- [X] AM Armenia .....
- [X] AT Austria .....
- [X] AU Australia .....
- [X] AZ Azerbaijan
- [X] BA Bosnia and Herzegovina .....
- [X] BB Barbados
- [X] BG Bulgaria .....
- [X] BR Brazil .....
- [X] BY Belarus .....
- [X] CA Canada
- [X] CH and LI Switzerland and Liechtenstein
- [X] CN China .....
- [X] CU Cuba .....
- [X] CZ Czech Republic .....
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- [X] EE Estonia .....
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- [X] GM Gambia
- [X] GW Guinea-Bissau .....
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- [X] LC Saint Lucia
- [X] LK Sri Lanka
- [X] LR Liberia
- [X] LS Lesotho .....
- [X] LT Lithuania
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Check-boxes reserved for designating States (for the purposes of a national patent) which have become party to the PCT after issuance of this sheet:

- [X] ..... (GD) Grenada .....
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Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)*

See Notes to the request form

Supplemental Box *If the Supplemental Box is not used, this sheet should not be included in the request.*

1. *If, in any of the Boxes, the space is insufficient to furnish all the information: in such case, write "Continuation of Box No. ..." [indicate the number of the Box] and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient, in particular:*

(i) *if more than two persons are involved as applicants and/or inventors and no "continuation sheet" is available: in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below;*

(ii) *if, in Box No. II or in any of the sub-boxes of Box No. III, the indication "the States indicated in the Supplemental Box" is checked: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant;*

(iii) *if, in Box No. II or in any of the sub-boxes of Box No. III, the inventor or the inventor/applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor;*

(iv) *if, in addition to the agent(s) indicated in Box No. IV, there are further agents: in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV;*

(v) *if, in Box No. V, the name of any State (or OAPI) is accompanied by the indication "patent of addition," or "certificate of addition," or if, in Box No. V, the name of the United States of America is accompanied by an indication "continuation" or "continuation-in-part": in such case, write "Continuation of Box No. V" and the name of each State involved (or OAPI), and after the name of each such State (or OAPI), the number of the parent title or parent application and the date of grant of the parent title or filing of the parent application;*

(vi) *if, in Box No. VI, there are more than three earlier applications whose priority is claimed: in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI;*

(vii) *if, in Box No. VI, the earlier application is an ARIPO application: in such case, write "Continuation of Box No. VI", specify the number of the item corresponding to that earlier application and indicate at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed.*

2. *If, with regard to the precautionary designation statement contained in Box No. V, the applicant wishes to exclude any State(s) from the scope of that statement: in such case, write "Designation(s) excluded from precautionary designation statement" and indicate the name or two-letter code of each State so excluded.*

3. *If the applicant claims, in respect of any designated Office, the benefits of provisions of the national law concerning non-prejudicial disclosures or exceptions to lack of novelty: in such case, write "Statement concerning non-prejudicial disclosures or exceptions to lack of novelty" and furnish that statement below.*

Pharma Mar, S.A., is applicant for (JP) Japan, (AU) Australia, (CA) Canada, (KR) Republic of Korea, (FI) Finland, (BR) Brazil, (MX) Mexico, (RU) Russian Federation, (UA) Ukraine, (NZ) New Zealand, (EP) All States, (AT) Austria, (CH and LI) Switzerland and Liechtenstein, (DE) Germany, (ES) Spain, (GB) United Kingdom, (LU) Luxembourg, (PT) Portugal, (SE) Sweden, (DK) Denmark.

Ruffles, Graham Keith is an applicant for (AP) ARIPO, (EA) Eurasian Patent, (OA) OAPI, National Patents in: (AL) Albania, (AM) Armenia, (AZ) Azerbaijan, (BA) Bosnia and Herzegovina, (BB) Barbados, (BG) Bulgaria, (BY) Belarus, (CN) China, (CU) Cuba, (CZ) Czech Republic, (EE) Estonia, (GE) Georgia, (GH) Ghana, (HU) Hungary, (IL) Israel, (IS) Iceland, (KE) Kenya, (KG) Kyrgyzstan, (KP) Democratic Peoples Republic of Korea, (KZ) Kazakstan, (LC) Saint Lucia, (LK) Sri Lanka, (LR) Liberia, (LS) Lesotho, (LT) Lithuania, (LV) Latvia, (MD) Republic of Moldova, (MG) Madagascar, (MK) The Former Yugoslav Republic of Macedonia, (MN) Mongolia, (MW) Malawi, (NO) Norway, (PL) Poland, (RO) Romania, (SD) Sudan, (SG) Singapore, (SI) Slovenia, (SK) Slovakia, (TJ) Tajikistan, (TM) Turkmenistan, (TR) Turkey, (TT) Trinidad and Tobago, (UG) Uganda, (UZ) Uzbekistan, (VN) Vietnam, (YU) Yugoslavia, (ID) Indonesia, (SL) Sierra Leone, (ZW) Zimbabwe, (GM) Gambia, (GW) Guinea-Bissau, (GD) Grenada, (HR) Croatia, (IN) India

Sheet No. 4.....

Box No. VI PRIORITY CLAIM

☐ Further priority claims are indicated in the Supplemental Box.

Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is: national application: country	regional application:* regional Office	international application: receiving Office
item (1) 18 Feb 1998 (18.2.98)	9803448.1	United Kingdom		
item (2)				
item (3)				

☒ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office)* identified above as item(s): 1

* *Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.*

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):*

ISA /

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority):*

Date *(day/month/year)* Number Country *(or regional Office)*

Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following number of sheets:

request	: 6
description (excluding sequence listing part)	: 6
claims	: 2
abstract	: 1
drawings	:
sequence listing part of description	:
Total number of sheets	: 15

This international application is accompanied by the item(s) marked below:

1. ☒ fee calculation sheet
2. ☐ separate signed power of attorney
3. ☒ copy of general power of attorney; reference number, if any:
4. ☐ statement explaining lack of signature
5. ☐ priority document(s) identified in Box No. VI as item(s):
6. ☐ translation of international application into (language):
7. ☐ separate indications concerning deposited microorganism or other biological material
8. ☐ nucleotide and/or amino acid sequence listing in computer readable form
9. ☒ other *(specify)*: Form 23/77

Figure of the drawings which should accompany the abstract:

Language of filing of the international application: English

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

ABLEWHITE ALAN J.

Ruffles, Graham Keith

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1. Date of actual receipt of the purported international application:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:
4. Date of timely receipt of the required corrections under PCT Article 11(2):
5. International Searching Authority (if two or more are competent): ISA /
6. ☐ Transmittal of search copy delayed until search fee is paid.

2. Drawings:
   - ☐ received:
   - ☐ not received:

For International Bureau use only

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The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ EP 13 September 1999

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

For International Preliminary Examining Authority use only	
Identification of IPEA	Date of receipt of DEMAND

Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION		Applicant's or agent's file reference: 545P78531
International application No.: PCT/GB99/00511	International filing date *(day/month/year)*: 18 February 1999 (18.02.1999)	(Earliest) Priority date *(day/month/year)*: 18 February 1998 (18.02.1998)

Title of invention: PHARMACEUTICAL FORMULATION OF A DIDEMNIN COMPOUND

Box No. II APPLICANT(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

Pharma Mar, S.A.
Calle de la Calera, 3
Polígono Industrial de Tres Cantos
28760 Tres Cantos
Madrid, Spain

Telephone No.:
Facsimile No.:
Teleprinter No.:

State *(that is, country)* of nationality: ES
State *(that is, country)* of residence: ES

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

Ruffles, Graham Keith
57-60 Lincoln's Inn Fields
London WC2A 3LS
United Kingdom

State *(that is, country)* of nationality: GB
State *(that is, country)* of residence: GB

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

Beijnen, Jacob Hendrik
The Netherland Cancer Institute/Slotervaart Hospital
Department of Pharmacology
Louwesweg 6
1066 EC Amsterdam
The Netherlands

State *(that is, country)* of nationality: NL
State *(that is, country)* of residence: NL

[X] Further applicants are indicated on a continuation sheet.

See Notes to the demand form

International application No.
PCT/GB99/00511

Continuation of Box No. II APPLICANT(S)

If none of the following sub-boxes is used, this sheet should not be included in the demand.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

Nuyen, Bastiaan
The Netherland Cancer Institute/Slotervaart Hospital
Department of Pharmacology
Louwesweg 6
1066 EC Amsterdam
The Netherlands

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
NL	NL

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

Henrar, Roland Elizabeth Cornelis
New Drug Development Office (NDDO)
Free University Hospital
Gebouw Zuid
Amstelveenseweg 601
1081 JC Amsterdam
The Netherlands

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
NL	NL

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

Gomez, Andres
Pharma Mar, S.A.
Calle de la Calera, 3
Poligono Industrial de Tres Cantos
28760 Tres Cantos
Madrid
Spain

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
ES	ES

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

Jimeno, Jose
Pharma Mar, S.A.
Calle de la Calera, 3
Poligono Industrial de Tres Cantos
28760 Tres Cantos
Madrid
Spain

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
ES	ES

☐ Further applicants are indicated on another continuation sheet.

See Notes to the demand form

International application No. PCT/GB99/00511

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is [X] agent [ ] common representative

and [X] has been appointed earlier and represents the applicant(s) also for international preliminary examination.

[ ] is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.

[ ] is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

Ruffles, Graham Keith
Marks & Clerk
57-60 Lincoln's Inn Fields
London WC2A 3LS
United Kingdom

Telephone No.: 0171-400-3000

Facsimile No.: 0171-404-4910

Teleprinter No.: 25311 EMANDC G

[ ] Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments:*

1. The applicant wishes the international preliminary examination to start on the basis of:

[X] the international application as originally filed

the description [ ] as originally filed
[ ] as amended under Article 34

the claims [ ] as originally filed
[ ] as amended under Article 19 (together with any accompanying statement)
[ ] as amended under Article 34

the drawings [ ] as originally filed
[ ] as amended under Article 34

2. [ ] The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.

3. [ ] The applicant wishes the start of the international preliminary examination to be postponed until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). *(This check-box may be marked only where the time limit under Article 19 has not yet expired.)*

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: English

[X] which is the language in which the international application was filed.
[ ] which is the language of a translation furnished for the purposes of international search.
[ ] which is the language of publication of the international application.
[ ] which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

Box No. V ELECTION OF STATES

The applicant hereby elects all eligible States *(that is, all States which have been designated and which are bound by Chapter II of the PCT)*

excluding the following States which the applicant wishes not to elect:

See Notes to the demand form

Sheet No. 4

International application No. PCT/GB99/00511

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:			For International Preliminary Examining Authority use only: received	not received
1. translation of international application	:	sheets	☐	☐
2. amendments under Article 34	:	sheets	☐	☐
3. copy (or, where required, translation) of amendments under Article 19	:	sheets	☐	☐
4. copy (or, where required, translation) of statement under Article 19	:	sheets	☐	☐
5. letter	:	sheets	☐	☐
6. other *(specify)*	:	sheets	☐	☐

The demand is also accompanied by the item(s) marked below:

1. [X] fee calculation sheet
2. [ ] separate signed power of attorney
3. [ ] copy of general power of attorney; reference number, if any:
4. [ ] statement explaining lack of signature
5. [ ] nucleotide and or amino acid sequence listing in computer readable form
6. [ ] other *(specify)*:

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

Godwin, Edgar James on behalf of
Ruffles, Graham Keith

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:
2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):
3. [ ] The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply. [ ] The applicant has been informed accordingly.
4. [ ] The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.
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International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
A61K 38/15, 9/08, 9/19

A1

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(22) International Filing Date: 18 February 1999 (18.02.99)

(30) Priority Data:
9803448.1 18 February 1998 (18.02.98) GB

(71) Applicant *(for AT AU BE BR CA CH CY DE DK ES FI FR GB GR IE IT JP KR LU MC MX NL NZ PT RU SE UA only)*: PHARMA MAR, S.A. [ES/ES]; Poligono Industrial de Tres Cantos, Calle de la Calera, 3, E–28760 Tres Cantos (ES).

(71) Applicant *(for all designated States except AT AU BE BR CA CH CY DE DK ES FI FR GB GR IE IT JP KR LU MC MX NL NZ PT RU SE UA US)*: RUFFLES, Graham, Keith [GB/GB]; 57–60 Lincoln's Inn Fields, London WC2A 3LS (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: BEIJNEN, Jacob, Hendrik [NL/NL]; (NL). NUYEN, Bastiaan [NL/NL]; (NL). HENRAR, Roland, Elizabeth, Cornelis [NL/NL]; New Drug Development Office (NDDO), Free University Hospital, Gebouw Zuid, Amstelveenseweg 601, NL–1081 JC Amsterdam (NL). GOMEZ, Andres [ES/ES]; Pharma Mar, S.A., Poligono Industrial de Tres Cantos, Calle de la Calera, 3, E–28760 Tres Cantos (ES). JIMENO, Jose [ES/ES]; Pharma Mar, S.A., Poligono Industrial de Tres Cantos, Calle de la Calera, 3, E–28760 Tres Cantos (ES).

(74) Agent: RUFFLES, Graham, Keith; Marks & Clerk, 57–60 Lincoln's Inn Fields, London WC2A 3LS (GB).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: PHARMACEUTICAL FORMULATION OF A DIDEMNIN COMPOUND

(57) Abstract

A stable pharmaceutical composition of a didemnin compound, comprises firstly a lyophilised didemnin preparation including water–soluble material and secondly a reconstitution solution of mixed solvents.

FOR THE PURPOSES OF INFORMATION ONLY

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PHARMACEUTICAL FORMULATION OF A DIDEMNIN COMPOUND

The present invention relates to a pharmaceutical formulation, and more particularly a pharmaceutical formulation of a didemnin compound.

THE BACKGROUND

US Patent 5,294,603 to Rinehart claims a pharmaceutical composition comprising a didemnin, in combination with a pharmaceutically acceptable carrier, excipient or diluent. In that patent, extensive results are given for testing for biological activity, notably assay results for cytotoxicity and antiviral activity.

THE PROBLEM

In practice, there are some difficulties in preparing pharmaceutical compositions of didemnin compounds suited for administration to patients, and there is especially a need for a stable parental pharmaceutical dosage form. More specifically, didemnin compounds such as dehydrodidemnin B, also known as aplidine, require mixing with bulking agents, such as mannitol, for optimal,

stable preparation of pharmaceutical dosage forms, in particular lyophilised preparations,

Certain bulking agents for this purpose, such as mannitol, require water for solubilisation, while drugs such as aplidine are poorly soluble in water. However, drug delivery to patients requires resuspending of the lyophilised materials before use.

THE INVENTION

The present invention solves the problem by providing a pharmaceutical composition of a didemnin compound, comprising firstly a lyophilised didemnin preparation including water-soluble materials and secondly a reconstitution solution of mixed solvents. The mixed solvents comprise an aqueous solvent, with the water serving to dissolve the water soluble material and the other solvent serving to dissolve the didemnin compound.

PREFERRED EMBODIMENTS

The pharmaceutical formulation of this invention is typically a stable parental pharmaceutical dosage form suited for reconstitution for administration to patients as an antitumor treatment. The invention solves the problem for drugs such as aplidine, which must be presented as lyophilised mixtures of two or more substances soluble in incompatible solvents. It preferably

provides, separately bottled or otherwise contained, a premixed three component surfactant/alkanol/water mixture of solvents. In order to allow for proper resuspension of such pharmaceutical dosage forms, the separately packaged solvent mixture is provided to be added to the dry lyophilised preparations containing the drug and water soluble substances such as mannitol, before administration for treatment of disease.

Preferred didemnin compounds for the pharmaceutical compositions of this invention include didemnins and didemnin derivatives, such as dehydrodidemnins, nordidemnins, didemnin congeners and didemnin analogs. The present invention is particularly directed at didemnins with limited water solubility, including for example dehydrodidemnin B, also known as aplidine.

The antitumour agent aplidine (dehydrodidemnin B) is a natural occurring cyclic depsipeptide isolated from the Mediterranean runicate *Aplidium albicans.* Aplidine has been characterised by using several chromatographic and spectrometric techniques. Solubility testing showed that aplidine exhibits poor aqueous solubility. Moreover, the long-term stability of aplidine in solution is currently unknown.

The lyophilised didemnin preparation is preferably prepared by freeze drying a didemnin/alkanol/water mix, especially using t-butanol as the alkanol. The alkanol/water mix suitably contains 25 to 60% v/v alkanol. A bulking agent such as mannitol can

also be included, though other conventional water-soluble additives may be included, known to be of utility in the preparation of such lyophilised dosage forms.

The reconstitution solution preferably comprises a surfactant/alkanol/water mix, especially using a nonionic surfactant and ethanol as the alkanol. The surfactant is suitably 10 to 25% v/v of the mix; the alkanol is suitably 10 to 25% v/v of the mix; and the water is suitably 50 to 80% v/v of the mix.

EXAMPLES

Freeze-drying was performed from a 1.0 mg/ml solution aplidine in 40% v/v t-butanol in water for injection ("WFI) containing 25 mg/ml mannitol as bulking agent. Differential scanning calorimetry studies were conducted to determine the freeze-drying cycle parameters. The prototype, containing 1.0 mg aplidine and 25 mg mannitol per vial was found to be the optimal formulation in terms of solubility, length of the freeze-during cycle and dosage requirements.

A solution composed of 15/15/70% (v/v/v) Cremophor EL/ethanol absolute/WFI was found to the optimal reconstitution solution, Cremophor EL being a glycerol-polyethylene glycol ricinoleate available from BASF in Germany.

Dilutions of reconstituted product with normal saline up to 1:200 showed it to be stable for at least 24 hours after preparation. Quality control of the freeze-dried formulation demonstrated that the manufacturing process does not change the integrity of aplidine. Shelf-life data, available thus far, show that the formulation is stable for at least 6 months when stored at +4°C in the dark.

Thus, the preferred aplidine product of this invention is a dual-package containing:

an injection vial containing aplidine 1 mg/vial lyophilized product, and an injection vial containing 2 ml of 15/15/70% (v/v/v) Cremophor EL/ethanol/water as reconstruction solution.

The use of 15/15/70% (v/v/v) Cremophor EL/ethanol/water as reconstitution solution for a lyophilized product is unprecedented. Thus far, the combination of Cremophor EL/ethanol in commercial available products has been used exclusively as solution vehicle (e.g., taxol or cyclosporine).

The development of the Cremophor EL/ethanol/water vehicle provides a potent co-solvent/surfactant system which can be applied as reconstitution solution in future drug formulations and allows the addition of a water soluble bulking agent such as mannitol. Furthermore, by decreasing the relative amount of Cremophor EL, a less toxic vehicle is created.

The manufacturing procedure of the lyophilized product has also a special feature. Normally, freeze-drying of a drug is performed from a drug solution in water. In the case of aplidine, a 40% (v/v) t-butanol/water mixture is preferably used as freeze-drying medium. Although previously described (e.g. rhizoxin), freeze-drying from a 40% t-butanol/water mixture is not common practice.

In conclusion, the combination of lyophilisation of a drug from a t-butanol/water mixture and the subsequent reconstitution of the lyophilized product with 15/15/70% (v/v/v) Cremophor EL/ethanol/water is unique.

CLAIMS:

1. A pharmaceutical composition of a didemnin compound, comprising firstly a lyophilised didemnin preparation including water-soluble material and secondly a reconstitution solution of mixed solvents.

2. A didemnin composition according to claim 1, intended for reconstitution for administration to patients as an antitumor treatment.

3. A didemnin composition according to claim 1 or 2, wherein the didemnin is chosen from didemnins, dehydrodidemnins, nordidemnins, didemnin congeners and didemnin analogs.

4. A didemnin composition according to claim 3, wherein the didemnin compound is aplidine.

5. A didemnin composition according to any preceding claim, wherein the reconstitution solution comprises an alkanol/water mix.

6. A didemnin composition according to claim 5, wherein the reconstitution solution includes a nonionic surfactant.

7. A didemnin composition according to claim 6, wherein the nonionic surfactant is 10 to 25% v/v of the solution; the

alkanol is ethanol and is 10 to 25% v/v of the solution; and the water is 50 to 80% v/v of the solution.

8. A didemnin composition according to any preceding claim, which comprises a vial of lyophilised didemnin preparation including a water-soluble bulking agent, and a separate vial of a premix of non-ionic surfactant/ethanol/water.

9. A method of preparing a pharmaceutical composition of a didemnin compound, which comprises freeze drying a didemnin/water-soluble additive/alkanol/water mix to provide a lyophilised first component, and separately providing an alkanol/water mix as reconstitution solution.

10. A method according to claim 9 wherein the alkanol in the mix is t-butanol.

11. A method according to claim 9 or 10 wherein the amount of alkanol in the alkanol/water mix is 25 to 60% v/v.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 99/00511

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K38/15 A61K9/08 A61K9/19

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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A	US 5 462 726 A (N.J. LODGE) 31 October 1995 (1995-10-31) column 5, line 62 - line 66; claims 1-5; example 4	1-11

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 July 1999	30/07/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Ryckebosch, A

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Information on patent family members

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